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Original Article

Outcomes after early treatment with hydroxychloroquine and azithromycin: An analysis of a database of 30,423 COVID-19 patients

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ABSTRACT

Background: Many studies have evaluated the use of hydroxychloroquine in COVID-19. Most retrospective observational studies demonstrate a benefit of using HCQ on mortality, but not most randomized clinical trials.
Methods: We analyzed raw data collected from a cohort of 30,423 patients with COVID-19 cared for at IHU Méditerranée Infection in Marseille France and extracted from the DRYAD open data platform. We performed univariate and multivariable logistic regressions with all-cause mortality within six weeks. Multivariable logistic regressions were adjusted for sex, age group (<50, 50–69, 70–89 and > 89 years), periods (or variants), and type of patient management.
Results: Among 30,202 patients for whom information on treatment was available, 191/23,172 (0.82%) patients treated with HCQ-AZ died, compared to 344/7030 (4.89%) who did not receive treatment with HCQ-AZ. HCQ-AZ therapy was associated with a lower mortality than treatment without HCQ-AZ (odds ratio (OR) 0.16; 95% confidence interval (CI), 0.14–0.19). After adjustment for sex, age, period, and patient management, HCQ-AZ was associated with a significantly lower mortality rate (adjusted OR (aOR) 0.55, 95% CI 0.45–0.68). On a subsample of 21,664 patients with available variant information, results remained robust after adjustment on sex, age, patient management and variant (aOR 0.55; 95% CI 0.44–0.69). On a subsample of 16,063 patients, HCQ-AZ was still associated with a significantly lower mortality rate (aOR 0.47, 95%CI 0.29–0.75) after adjustment for sex, age, period, patient management, vaccination status and comorbidities.
Conclusion: Analysis of this large online database showed that HCQ-AZ was consistently associated with the lowest mortality.

1. Introduction

The treatment for COVID 19 has given rise to more controversy than the treatment of any infectious disease prior to this epidemic [1]. While experimental randomized controlled trials (RCT), the biggest of which to date are RECOVERY [2] and SOLIDARITY [3], do not demonstrate any benefit of treating COVID-19 with hydroxychloroquine, the biggest observational retrospective studies demonstrate a benefit in terms of reducing mortality [4,5]. Many RCTs, particularly those conducted during outbreak were published or stopped at an early stage, despite the fact that the calculated sample size of patients had not been achieved. Consequently, the underpowered nature of the studies means it is not possible to reach conclusions as to the lack or otherwise of efficacy [6–8]. Moreover, in these conditions, where patient recruitment and standard of care is likely to vary widely between recruiting centers, the Simpson paradox would arise. Consequently, RCTs would have beneficiated from non-aggregated data analysis to check the effect of hydroxychloroquine treatment in each center [9]. In contrast, the retrospective aspect of observational studies suffers from a selection bias and misclassification or an information bias for which multivariable regression, propensity score matching, and other statistical methods, while not perfect, would improve the selection bias and reinforce internal validity [10,11]. Moreover, conclusions of monocentric studies might not be generalizable, and often apply on the population studied only. Finally, there is little evidence of significant effect estimate differences between observational studies and RCTs. Factors other than the study design *per se* need to be considered when exploring reasons for a lack of agreement between the results of RCTs and observational studies [12]. Because RCTs and other prospective trials are no longer possible due to the disappearance of the epidemic, it is essential to collect

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Table 1
Baseline characteristics (n = 30,423).

	All		HCQ-AZ[a]			No HCQ-AZ[a]		P[b]	Missing data	
	n	%col	n	%col	%row	n	%col		n	%col
N	30423		23172			7030			221	
Men	14505	47.7	11077	47.8	76.4	3312	47.1	0.310	116	52.5
Age										
<50	15925	52.3	12981	56.0	81.5	2805	39.9	<.001	139	62.9
50-69	10786	35.5	8154	35.2	75.6	2560	36.4	0.060	72	32.6
70-89	3413	11.2	1934	8.3	56.7	1470	20.9	<.001	9	4.1
>89	299	1.0	103	0.4	34.4	195	2.8	<.001	1	0.5
Period										
1–2020/03/03–2020/06/15	4132	13.6	3637	15.7	88.0	459	6.5	<.001	36	16.3
2–2020/06/16–2020/09/20	3269	10.7	2292	9.9	70.1	880	12.5	<.001	97	43.9
3–2020/09/21–2020/11/22	4322	14.2	2788	12.0	64.5	1458	20.7	<.001	76	34.4
4–2020/11/23–2021/03/21	5906	19.4	4536	19.6	76.8	1362	19.4	0.709	8	3.6
5–2021/03/22–2021/06/27	5621	18.5	4393	19.0	78.2	1225	17.4	0.004	3	1.4
6–2021/06/28–2021/09/21	4624	15.2	3752	16.2	81.1	871	12.4	<.001	1	0.5
7–2021/09/22–2021/12/31	2549	8.4	1774	7.7	69.6	775	11.0	<.001	0	0.0
SARS-CoV-2 variants (nmiss = 8759) [c]and periods	18874		15035			3767			72	
A (Wuhan)	4079	18.8	3598	21.1	88.2	449	9.9	<.001	32	28.1
B.1.160 (Marseille 4)	4445	20.5	3176	18.6	71.5	1231	27.3	<.001	38	33.3
B.1.7.7 (UK)	5035	23.2	3988	23.4	79.2	1045	23.1	0.708	2	1.8
B.1.617.2 (Delta)	5315	24.5	4273	25.1	71.7	1042	23.1	0.006	0	0.0
Outpatients	26638	87.6	21135	91.2	79.3	5282	75.1	<.001	221	100.0
Inpatients	4538	14.9	2530	10.9	55.8	2008	28.6	<.001	0	0.0
Intensive care unit transfer	544	1.8	321	1.4	59.0	223	3.2	<.001	0	0.0
Death[d]	535	1.8	191	0.8	35.7	344	4.9	<.001	0	0.0

[a] HCQ: Hydroxychloroquine, AZ: Azithromycin.
[b] Chi-squared test (HCQ-AZ vs. no HCQ-AZ).
[c] Variants with n < 4000 are not displayed.
[d] All-cause deaths within six weeks.

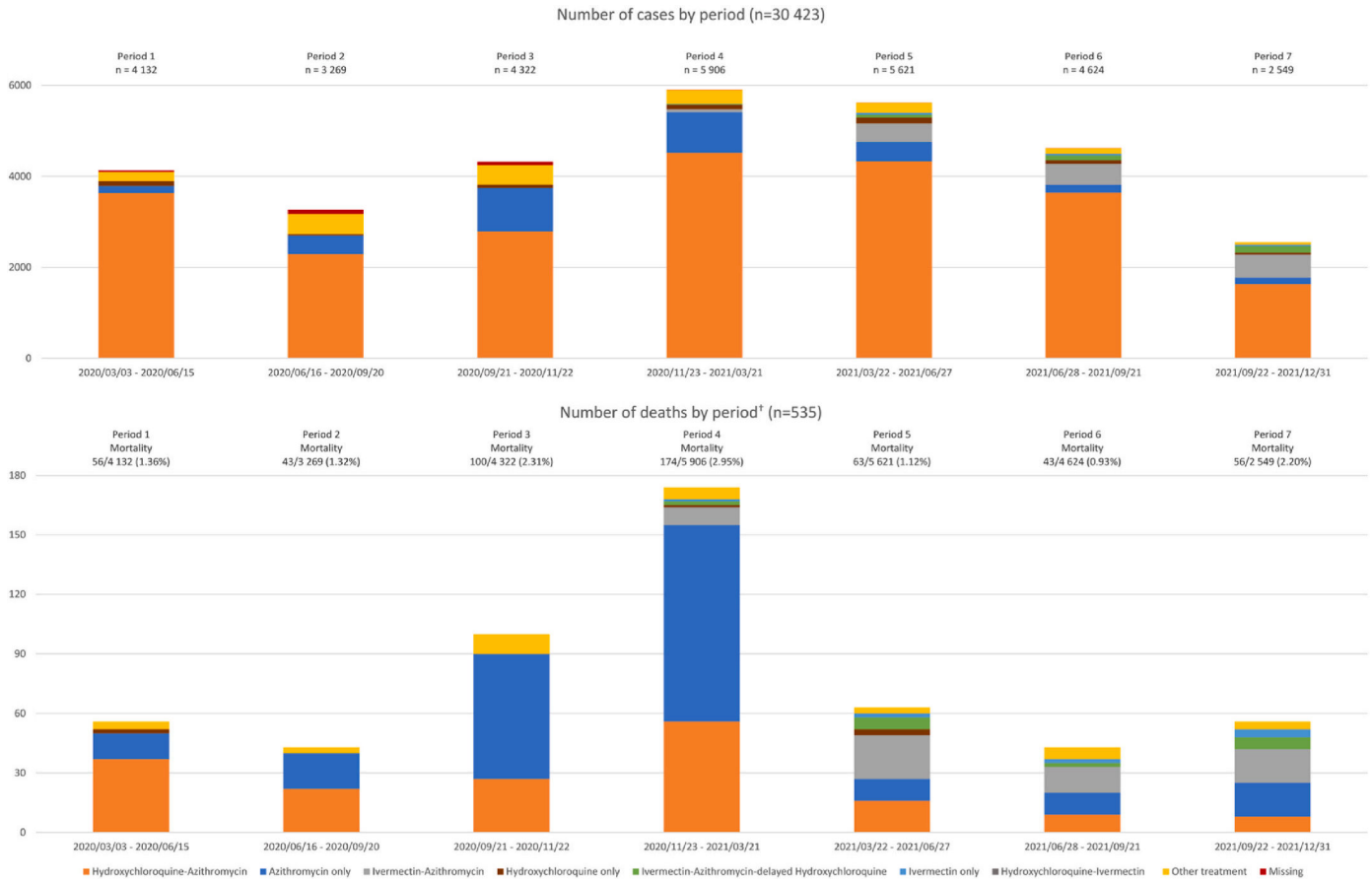

Fig. 1. Number of cases by period (n = 30,423).

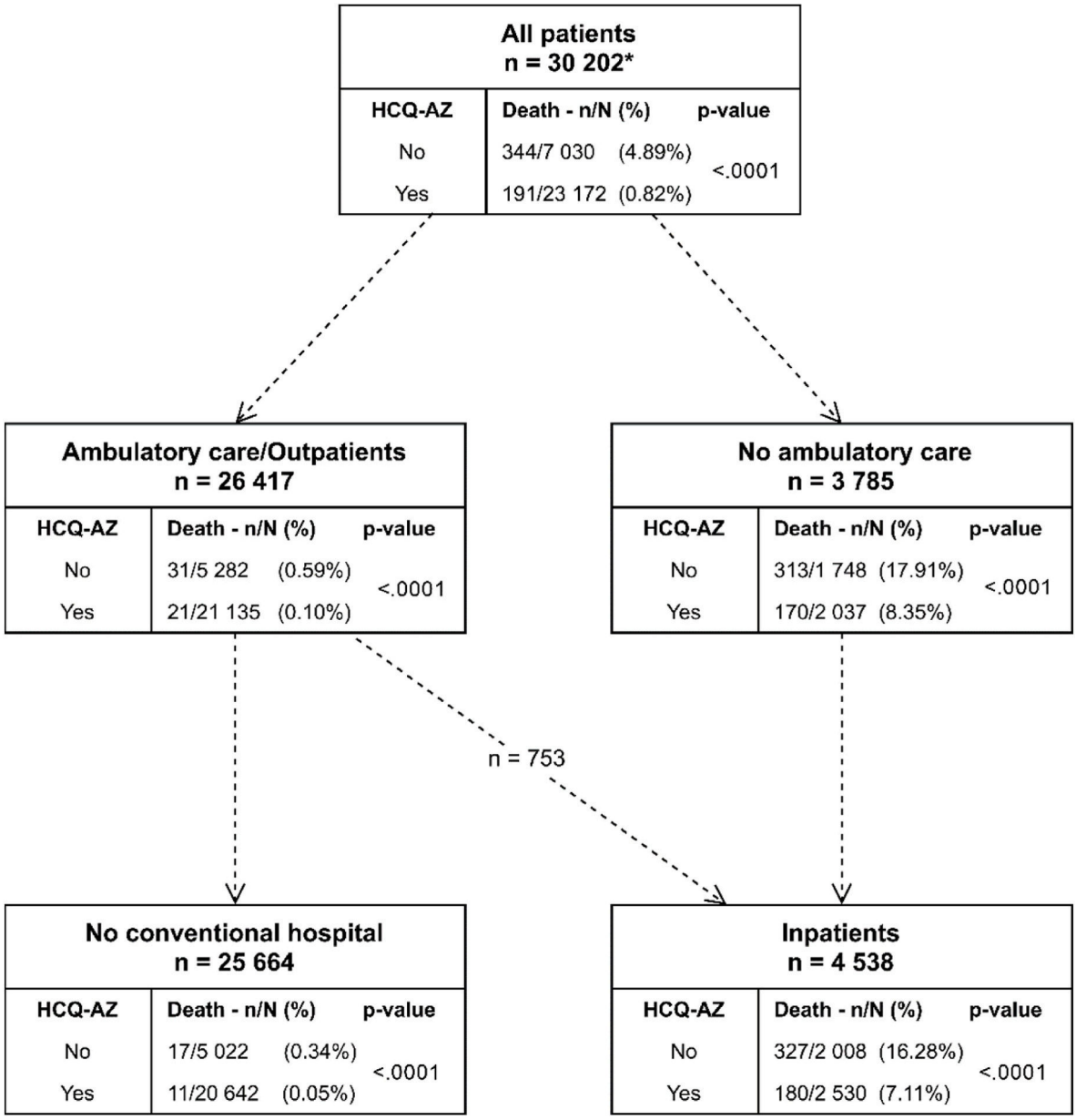

Fig. 2. Flowchart of healthcare pathways (n = 30,202*)
*221 patients were excluded because of missing treatment data.

retrospective data and make them available to the scientific and medical community. In this study, we aim to analyze the factors associated with death at six weeks according to variables contained in a database which is freely available under a Creative Commons Zero (CC O) license, including data on a cohort of 30,423 patients [13,14]. While being aware of the disadvantages of observational studies, we believe that this study on more than 30,000 patients, the largest monocentric cohort worldwide, could provide important insights for policy makers on the treatment of COVID with the hydroxychloroquine-azithromycin combination.

2. Methods

2.1. Data

The construction, quality control and regulatory aspects of the database used in this study were recently described in detail elsewhere [15]. Briefly, data from 30,423 patients with COVID-19 cared for at IHU Méditerranée Infection in Marseille France were provided from the electronic patient record (EPR) which centralizes all medical information in the hospital. Inclusion criteria were all patients over the age of 18, with PCR-proven COVID-19 who received treatment in the hospital, either as an inpatient or as an outpatient, between March 2, 2020 and December 31, 2021. Treatment data were extracted from medical records and from pharmacy files. The rational for the off-label prescription of AZ and/or HCQ has been reported elsewhere [16]. Deaths were recorded on the EPRs but also in the French National Death Registry (INSEE) database. All data were anonymized. The final dataset available in the online database contained the following variables: age (range), gender, pandemic period, outpatient, inpatient, HCQ (hydroxychloroquine), AZ (azithromycin), IVM (ivermectin), virus genomic variant, ICU treatment, time of death, vaccination status, obesity, diabetes, blood pressure, asthma, cancer, immunodeficiency, chronic cardiac disease, chronic obstructive pulmonary disease (COPD), and autoimmune disease. A description of the file structure is reported in detail in the "read me" file in the database folder. For this analysis, raw

Table 2
Multivariable model of COVID-19 mortality among patients treated in our center 2020–2021 (n = 30,202[a]).

		Model A			p	Model B				
		OR 95% CI[b]	p	aOR, 95% CI[c]			OR, 95% CI[‡]	*P*	aOR, 95% CI[c]	*P*
Sex (ref. Women)	Men			1.61 1.32–1.96	<.001				1.61 1.32–1.96	<.001
Age (Ref. <50)	50–69			6.52 3.21–13.3	<.001				6.47 3.19–13.1	<.001
	70–89			40.4 20.2–80.7	<.001				39.4 19.7–78.6	<.001
	>89			89.9 43.0–188	<.001				86.4 41.4–180	<.001
Period (Ref. 2020/03/03-2–020/06/15)	2020/06/16-2–020/09/20			0.94 0.61–1.46	0.787				0.92 0.59–1.43	.704
	2020/09/21-2–020/11/22			1.21 0.83–1.76	0.313				1.16 0.80–1.69	.438
	2020/11/23-2–021/03/21			1.96 1.39–2.77	<.001				1.90 1.34–2.68	<.001
	2021/03/22-2–021/06/27			1.06 0.71–1.58	0.787				0.99 0.65–1.50	.958
	2021/06/28-2–021/09/21			1.13 0.72–1.76	0.599				1.06 0.67–1.69	.789
	2021/09/22-2–021/12/31			1.27 0.83–1.95	0.262				1.22 0.78–1.91	.395
Outpatients (ref. No)	Yes			0.05 0.04–0.07	<.001				0.05 0.04–0.07	<.001
Treatment (ref. HCQ-AZ[d] (n = 23,172))	HCQ-AZ vs. No HCQ-AZ[d] (n = 7,030)	0.16 0.14–0.19	<.001	0.55 0.45–0.68	<.001	HCQ-AZ vs. AZ-only[d] (n = 3144)	0.10 0.07–0.13	<.001	0.51 0.35–0.72	<.001
						HCQ-AZ vs. IVM-AZ[d] (n = 1434)	0.17 0.11–0.27	<.001	0.54 0.31–0.97	.029
						HCQ-AZ vs. HCQ-only[d] (n = 566)	0.67 0.20–2.26	.974	0.85 0.22–3.25	1.000
						HCQ-AZ vs. IVM-AZ-delayed HCQ[d] (n = 329)	0.15 0.07–0.33	<.001	0.44 0.17–1.15	.157
						HCQ-AZ vs. IVM-only[d] (n = 98)	0.07 0.03–0.21	<.001	0.50 0.15–1.72	.692
						HCQ-AZ vs. HCQ-IVM[d] (n = 17)	0.27 0.00–23.9	.988	0.93 0.00–178	1.000
						HCQ-AZ vs. Other treatment (n = 1771)	0.37 0.21–0.64	<.001	0.49 0.26–0.93	.018

Tukey's correction was used to calculate *P* values and odds ratios for the treatment group variables (model B).
[a] A total of 221 patients were excluded due to missing treatment data (see Table 1).
[b] Crude odds ratio with 95% confidence interval.
[c] Adjusted odds ratio with 95% confidence interval.
[d] HCQ: Hydroxychloroquine, AZ: Azithromycin, IVM: Ivermectin.

data were downloaded from DRYAD, https://doi.org/10.5061/dryad.ksn02v78v.

2.2. Statistical analysis

As the aim of this study was to test whether HCQ-AZ was associated with a different mortality compared to other treatments, we first compared patients treated with and without the HCQ-AZ combination. Then, the role of each individual drug (HCQ, AZ or IVM) was analyzed regardless of the prescription of any of the other two drugs. In this approach, each drug was included as a binary covariate (yes/no) in the models. We performed univariate and multivariable logistic regressions with death as the outcome. Multivariate logistic regressions were adjusted for sex, age groups (<50, 50–69, 70–89 and > 89 years), periods (or variants), and type of patient management (inpatient/outpatient). We also performed stratified multivariable logistic regressions according to these covariates. Given that the French National Death Registry [17] is exhaustive, we considered that there were no missing data regarding outcomes. No data was missing regarding sex or period of admission. Treatment data were missing for a total of 221 patients. Since the proportion of patients with missing treatment data was very low (0.7%), they were excluded from the univariate and multivariable analyses of associations between treatment and death. Information on a total of 14,360 patients (47.2%) was missing regarding their vaccination status and comorbidities, and information on SARS-CoV-2 variant was missing or unknown for 8,759 patients (28.8%). Comorbidities, vaccinations, and variants were used as covariates in different subgroup analyses. A two-sided *P* value of less than 0.05 was considered to be statistically significant. Statistical analyses were carried out using SAS 9.4 statistical software (SAS Institute, Cary, NC). The primary outcome was six-week all-cause mortality.

2.3. Ethics

This study is an analysis of anonymized data which is freely available on under a Creative Commons license on the DRYAD platform [13], and the Science Data Bank [14]. IRB clearance for this database analysis was approved by the IHU Méditerranée infection independent ethics committee (No. 2021-015).

3. Results

3.1. Participants

The database we analyzed contain data from 30,423 patients, and were collected between March 2, 2020, and December 31, 2021. Due to the anonymization process of the database, the mean and median age values were not available. The distribution of patients by age range and

Table 3
Association between treatment (HCQ-AZ vs. no HCQ-AZ) and six-week mortality, multivariate logistic regression (n = 16,063).

		aOR, 95% CI[a]	*P*
Sex (ref. Women)	Men	1.71 1.05–2.78	.0307
Age (Ref. <50)	50–69	12.14 2.43–60.62	.0024
	>69[b]	73.63 14.78–366.87	<.0001
Period (Ref. 2020/03/03–2020/06/15)	2021/03/22–2021/06/27	0.69 0.38–1.23	.2089
	2021/06/28–2021/09/21	1.34 0.69–2.60	.3892
	2021/09/22–2021/12/31	0.88 0.42–1.84	.7357
Outpatients (ref. No)	Yes	0.11 0.07–0.18	<.0001
Vaccination (Ref. No)	Yes	0.29 0.12–0.67	.0041
Obesity (Ref. No)	Yes	2.01 1.23–3.29	.0057
High blood pressure (Ref. No)	Yes	1.37 0.83–2.24	.2150
Asthma (Ref. No)	Yes	0.76 0.26–2.23	.6197
Diabetes (Ref. No)	Yes	1.32 0.77–2.27	.3145
Autoimmune diseases (Ref. No)	Yes	0.69 0.23–2.05	.5043
Cancer (Ref. No)	Yes	1.34 0.65–2.74	.4278
Chronic cardiac disease (Ref. No)	Yes	1.20 0.60–2.41	.6098
Immunodeficiency (Ref. No)	Yes	4.01 1.69–9.50	.0016
COPD (Ref. No)	Yes	2.93 1.29–6.64	.0100
Treatment (ref. No HCQ-AZ[c] (n = 3115))	HCQ-AZ[c] (n = 12,945)	0.47 0.29–0.76	.0020

This subgroup was mainly composed of outpatients (95%) included only in 2021. Five percent of inpatients were patients who presented at our day hospital and were directly hospitalized the same day.

[a] Adjusted odds ratio with 95% confidence interval.

[b] The ">89" age group (n = 55) was merged with the "70–89" age group.

[c] HCQ: Hydroxychloroquine, AZ: Azithromycin, IVM: Ivermectin.

the demographic characteristics of the 30,423 included patients are detailed in Table 1. Some 47.7% of patients were male. Of the 30,423 patients, treatment information was available for 30,202 of them (99.3%), including 25,664 outpatients (84.9 %) and 4538 inpatients (15.1%).

3.2. All-cause mortality within six weeks

According to INSEE, there were 535 all-cause deaths within six weeks of diagnosis, including 52 who were initially managed as outpatients and 483 who were hospitalized in the standard way, without initial outpatient treatment. Among the included variables, age was the strongest risk factor for death. Male sex was a risk factor for death (men 2.2%, women 1.3%, Chi-squared test $P < 10^{-4}$). A peak of mortality was observed during period 4 (winter 2020/2021) at 2.95% (17.2% for inpatients) and a minimum was observed in period 6 (July to September 2021) at 0.93% (Fig. 1). Among the four major variants, the B.1.160 variant, which predominated during period 4, was associated with the highest mortality (3.9% vs. 1.3%, Chi-squared test $P < .0001$).

3.3. Association between treatment regimen and mortality

Of the 30,202 patients for whom treatment information was available, 191/23,172 patients (0.82%) treated with HCQ-AZ died, compared to 344/7,030 patients (4.89%) who did not receive HCQ-AZ (Fig. 2). Overall, HCQ-AZ therapy was associated with a lower mortality than treatment without HCQ-AZ (OR 0.16; 95% CI, 0.14–0.19). After adjustment for sex, age, period, and type of patient management (inpatient/outpatient), HCQ-AZ continued to be associated with a significantly lower mortality rate (aOR 0.55; 95% CI, 0.45–0.68) (Table 2). This was confirmed to be independent of the viral variant among 21,664 patients with available variant information (aOR 0.55; 95% CI, 0.44–0.69), and independent of comorbidities and vaccination status among 16,063 patients with available information for these covariables (aOR 0.47: 95% CI, 0.29–0.75) (Table 3). Overall mortality among outpatients treated with HCQ-AZ was extremely low (21/21135 (0.10%)), with no significant variation between periods and never exceeded 0.14% in any epidemic period.

Among inpatients and outpatients, the association between the treatment variable (HCQ-AZ) and outcome was not significantly different according to sex, period or variant (two-way interaction terms were not statistically significant). This contrasts with the fact that prescription rates changed significantly over time among inpatients. However, the association was significantly different according to patient care setting and age, with a maximal effect size among outpatients aged between 50 and 89 years (Fig. 3).

Comparing HCQ-AZ with all other different combinations of treatment, mortality was never significantly different when HCQ was used from the outset in the comparator group (HCQ only or HCQ-IVM) (Fig. 4). This led us to analyze the role of each drug independently. A total of 23,755 patients (78.7%) were administered a regimen with HCQ compared to 6447 patients (21.3%) who did not receive this drug. A total of 27,750 patients (91.9%) were administered AZ compared to 2,452 (8.1%) who were not. A total of 1,878 patients (6.2%) were administered a regimen with IVM compared to 28,545 patients (93.8%) who were not. When each drug was included as a binary covariate (yes/no) in the models, no difference in survival was found for AZ (aOR 0.97, $P = .861$) or IVM (1.08, $P = .633$). Only HCQ was associated with lower mortality (aOR 0.55, 0.44–0.68, $P < .0001$), and this was confirmed both for outpatients (aOR 0.31; 95% CI, 0.16–0.59, $P = .0004$) and inpatients (aOR 0.52; 0.42–0.65, $P < .001$) (Table 4).

4. Discussion

Among the limitations of this analysis, the monocentric nature of the cohort may have meant that the population of this center differed from the populations of other centers. When this population is compared with the biggest multicenter retrospective study published to date on the topic [18], the two populations are very similar in terms of age (0.4% aged >89 years old vs 0.6% aged >85 years old), however the number of men was lower in this population (47.8% vs 50.3 %, $P < .001$) as well were patients with hypertension (11.1% vs 14.0%, $P < .001$) or underlying respiratory diseases (7.6% vs 8.7%, $P = .005$). In contrast, the prevalence of obesity (19.7% vs 1.67%, $P < .001$) and cancer (4.0% vs 0.6%, $P < .001$) was significantly higher in this population. The prevalence of diabetes was comparable between the two studies (5.2% vs 5.8%, $P = .057$). The monocentric nature of the study might limit the generalizability of the findings, but this design might also reinforce internal validity [11,19]. Besides the limitation of patient selection, there is also the limitation of some physicians being outliers in the institution itself, perhaps thus leading to other subtle additional variations in patient care. Non-prescription of HCQ was previously reported in details, the first reason being not proposed by the physician, then, patient with cardiac contra-indication, patient refusing the treatment, patient with potential risk for interaction and others [20]. Moreover, the monocentric nature of this study attenuates the selection bias in relation with a common standard of care [21]. The role of severity of the disease in the outcome is also clearly a limitation of this analysis and, unfortunately, cannot be analyzed in this database, because the NEWS score is not available. However, an article was previously published on the first 3, 737 patients followed up in this center in which the NEWS score was available. A propensity score was calculated using multivariable logistic regression in order to balance the two treatment groups on age, comorbidities, and the NEWS score. The significant association between treatment with HCQ-AZ≥3days and reduction of risk of death was confirmed, by two different propensity score methods (propensity score matching and inverse probability weighting) showing that this association was independent of age, comorbidities, and severity of the disease [20].

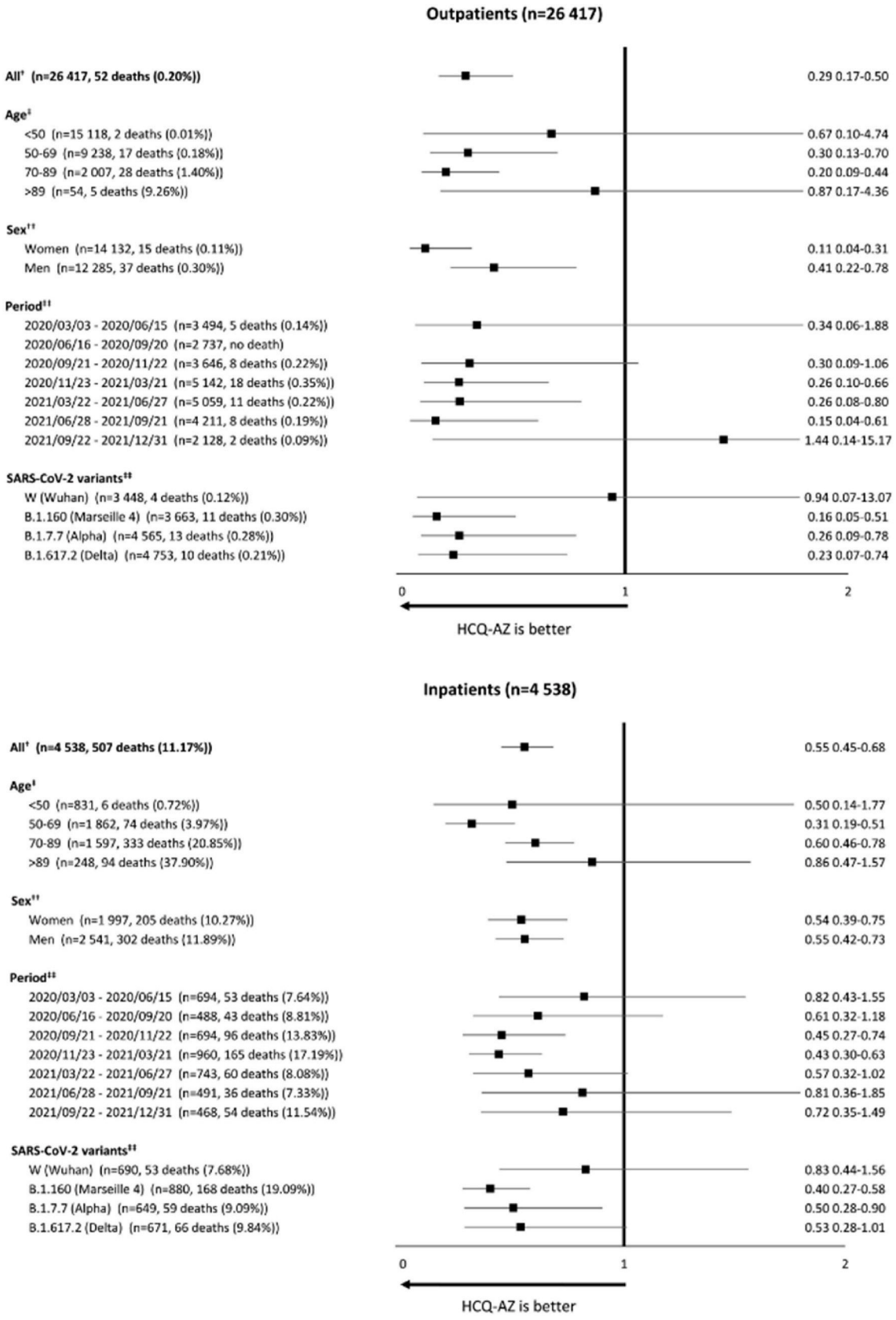

Fig. 3. Forest plot of the association between HCQ-AZ and six-week mortality
†: Sex-, age- and period-adjusted odds ratio with 95% CI. ‡: Sex- and period-adjusted odds ratio with 95% CI. ††: Age- and period-adjusted odds ratio with 95% CI. ‡‡: Sex- and age-adjusted odds ratio with 95% CI.

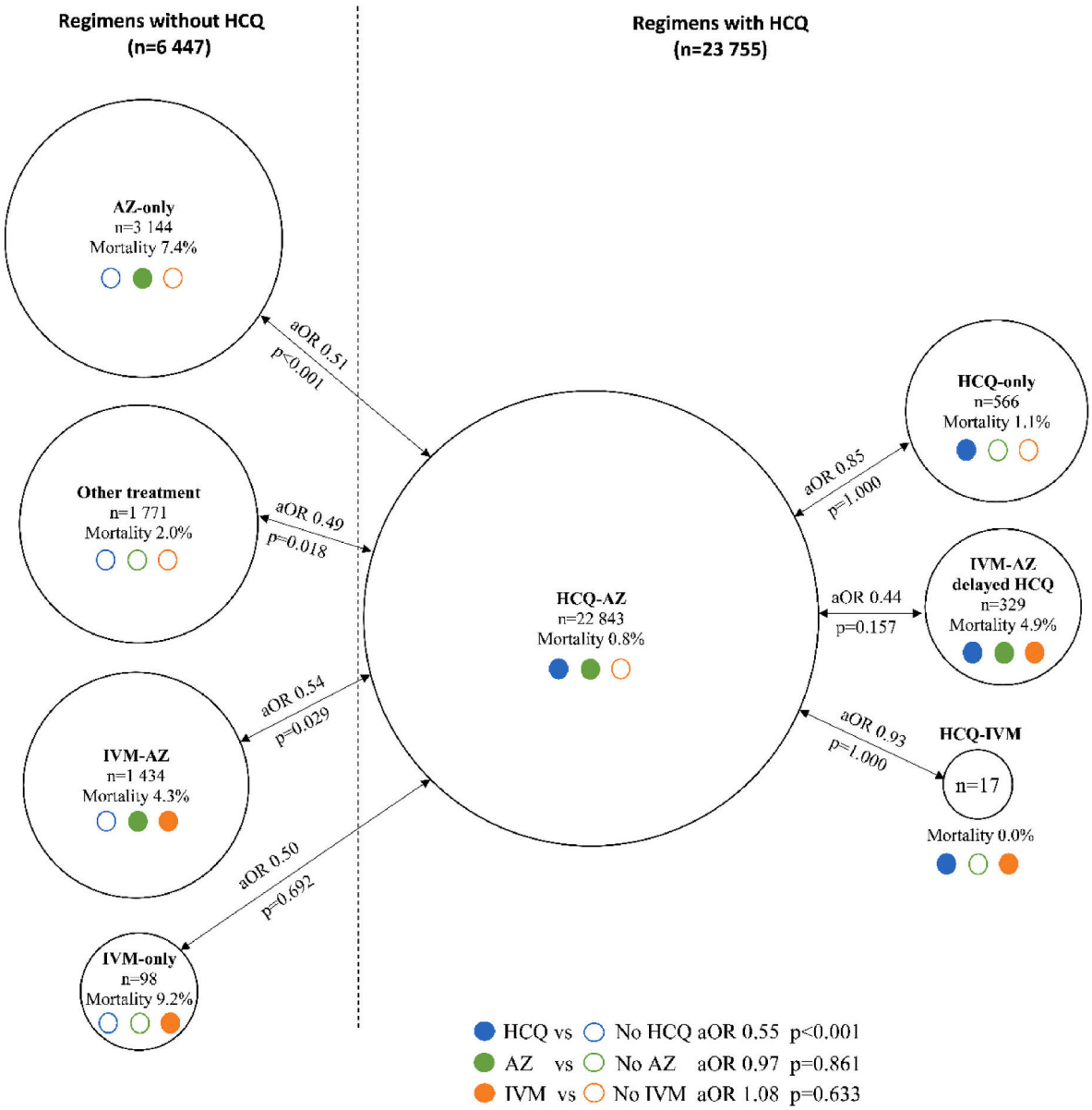

Fig. 4. Summary of comparisons between treatment groups and effect on mortality associated with each antiviral drug (n = 30,202)
HCQ: Hydroxychloroquine, AZ: azithromycin, IVM: ivermectin. aOR: adjusted odds ratio. Detailed results with 95% confidence intervals are available in the main text, Tables 1 and 2

Health policy on the use of hydroxychloroquine is supported by RCT results. Most of these RCTs do not report any benefits of using HCQ to reduce mortality in COVID patients. The largest two RCTs were RECOVERY (1,561 treated/3,155 controls) and SOLIDARITY (954 treated/909 controls) [2,3]. Both trials should be considered as late treatment trials as the randomization occurred upon hospital admission, including as an ICU patient. Both suffer from significant methodological problems, as the HCQ doses during the first 24 h (2400 mg) were four times higher than the highest recommended dose of 600 mg. Mortality was no different between the treatment and control groups, but a careful review of the causes of mortality in the two groups would be worth investigating. Other, smaller RCTs were performed in an attempt to demonstrate the efficacy of HCQ on mortality. These include the DisCoveRY trials which enrolled early moderate and late severe patients (150 treated/149 controls) and reported a 0.89 (0.36–1.92 (P = .66)) reduction in mortality at 28 days [6,22] but concluded that HCQ had no significant effect on mortality. This is inaccurate considering the calculated sample size of 620 patient per arm [6]. Indeed, in a study not reaching the predefined power it is impossible to know whether the absence of difference between the two groups is true or whether it is due to the lack power in the study [23]. Several other small RCTs are underpowered and reach inaccurate conclusions, but as a whole serve as a reference for policy makers [7]. In contrast, several large observational retrospective studies published in the literature, including a total of 47,516 patients report a benefit of using HCQ on the mortality of COVID-19 patients [4,5,16,18]. The number of patients involved in these studies largely overweighs the number of patients included in RCTs. Interestingly, these observational studies report that HCQ is associated with survival and the effect is greater in early treatment (**Supplementary Data Table**). Unfortunately, few if any of the RCTs that have attempted to demonstrate the efficacy of HCQ on COVID-19 patients were run with an appropriate methodology. Inadequate target (late treatment), excessive dosage of the drug, or inappropriate study power were the main troubles. While observational studies have also confounding factors, as discussed above, significant effect estimate differences between RCTs and observational studies are more likely to be linked to the

Table 4
Effect of HCQ on COVID-19 mortality: Multivariable model with HCQ, AZ and IVM included as individual covariates (all patients with available treatment data, n = 30,202[a]).

		aOR, 95% CI[b]	*P*
Sex (ref. Women)	Men	1.61 1.32–1.96	<.0001
Age (ref. <50)	50–69	6.47 3.18–13.14	<.0001
	70–89	39.47 19.75–78.91	<.0001
	>89	87.61 41.93–183.06	<.0001
Period (Ref. 2020/03/03-2–020/06/15)	2020/06/16-2–020/09/20	0.93 0.60–1.44	.7382
	2020/09/21-2–020/11/22	1.19 0.82–1.73	.3578
	2020/11/23-2–021/03/21	1.93 1.37–2.73	.0002
	2021/03/22-2–021/06/27	1.02 0.67–1.55	.9295
	2021/06/28-2–021/09/21	1.09 0.69–1.72	.728
	2021/09/22-2–021/12/31	1.22 0.77–1.91	.398
Outpatients (Ref. No)	Yes	0.05 0.04–0.07	<.0001
HCQ[c] (ref. No)		0.55 0.44–0.68	<.0001
AZ[c] (ref. No)		0.97 0.69–1.37	.8606
IVM[c] (ref. No)		1.08 0.78–1.49	.6326

[a] A total of 221 patients were excluded because of missing treatment data (see Table 1).
[b] Adjusted odds ratio with 95% confidence interval.
[c] HCQ: Hydroxychloroquine, AZ: azithromycin, IVM: ivermectin.

quality of the study than to its design [12]. In any case, since the epidemic has now vanished, it is no longer possible to conduct RCTs. Only observational studies can bring any more insights to support policy makers with repositioning of hydroxychloroquine in the treatment of COVID-19. This analysis of a database of 30,423 patients treated with hydroxychloroquine at a standard dosage of 200 mg three times a day shows that it reduces mortality in patients with COVID-19.

5. Conclusion

Overall, this study represents the largest single-center study evaluating HCQ-AZ in the treatment of COVID-19. Similarly, to other large observational studies, it concludes that HCQ would have saved lives. In a spirit of open science, we encourage investigators to re-analyze, similar FAIR (findable, accessible, interoperable, and reusable) databases and to report their findings.

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Transparency declaration

DR (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies in the study as planned (and, if relevant, registered) have been explained.

Declaration of competing interest

The authors have completed the Unified Competing Interest form (available on request from the corresponding author). DR declares grants, contracts, royalties and/or licenses from Hitachi High-Technologies Corporation, Tokyo, Japan. DR is a scientific board member of Eurofins. DR is founder and shareholder of four startups, none which have yet generated an income: a microbial culture company (Culture Top), two biotechnology companies (Techno-Jouvence and Gene and Green TK), and a rapid diagnosis of infectious diseases company (Pocramé). PB, MM and PMC declare no support from any organization for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nmni.2023.101188.

References

[1] Brouqui P, Drancourt M, Raoult D. There is no such thing as a Ministry of Truth and why it is important to challenge conventional "wisdom" - a personal view. New Microbes New Infect 2023 Sep;54:101155.
[2] RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of hydroxychloroquine in hospitalized patients with covid-19. N Engl J Med 2020 Nov 19;383(21):2030–40.
[3] WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, et al. Repurposed antiviral drugs for covid-19 - interim WHO solidarity trial results. N Engl J Med 2021 Feb 11;384(6):497–511.
[4] Million M, Lagier JC, Tissot-Dupont H, Ravaux I, Dhiver C, Tomei C, et al. Early combination therapy with hydroxychloroquine and azithromycin reduces mortality in 10,429 COVID-19 outpatients. Rev Cardiovasc Med 2021;22(3):1063.
[5] Nunez-Gil IJ, Ayerbe L, Fernandez-Perez C, Estrada V, Eid CM, Arroyo-Espliguero R, Romero R, Becerra-Munoz VM, Uribarri A, Feltes G, Trabattoni D, Molina M, Aguado MG, Pepe M, Cerrato E, Huang J, Astrua TC, Alfonso E, Castro-Mejia AF, Raposeiras-Roubin S, Buzon L, Paeres CE, Mulet A, Lal-Trehan N, Garcia-Vazquez E, Fabregat-Andres O, Akin I, Dascenzo F, Gomez-Rosado P, Ugo F, Fernandez-Ortiz A, Macaya C. Hydroxychloroquine and mortality in SARS-cov-2 Infection;the HOPE-covid-19 Registry. Anti-Infective Agents 2023:66–78.
[6] Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. Clin Microbiol Infect 2021 Dec;27(12):1826–37.
[7] Dubée V, Roy PM, Vielle B, Parot-Schinkel E, Blanchet O, Darsonval A, et al. Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial. Clin Microbiol Infect 2021 Aug;27(8):1124–30.
[8] Ulrich RJ, Troxel AB, Carmody E, Eapen J, Bäcker M, DeHovitz JA, et al. Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind randomized controlled trial in hospitalized patients. Open Forum Infect Dis 2020 Oct 1;7(10):ofaa446.
[9] Simpson EH. The interpretation of interaction in contingency Tables. J Roy Stat Soc B 1951;13(2):238–41.
[10] Bosdriesz JR, Stel VS, van Diepen M, Meuleman Y, Dekker FW, Zoccali C, et al. Evidence-based medicine-When observational studies are better than randomized controlled trials. Nephrology 2020 Oct;25(10):737–43.
[11] Nguyen VT, Engleton M, Davison M, Ravaud P, Porcher R, Boutron I. Risk of bias in observational studies using routinely collected data of comparative effectiveness research: a meta-research study. BMC Med 2021 Nov 23;19(1):279.
[12] Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 2014 Apr 29;(4):MR000034.
[13] Dryad | Data – Monocentric retrospective cohort of 30,423 COVID-19 patients [Internet]. [cited 2023 Jun 6]. Available from: https://datadryad.org/stash/dataset/doi:10.5061/dryad.ksn02v78v.

[14] Science data Bank. Science Data Bank Monocentric Retrospective Cohort of 30,423 COVID-19 Patients [Internet]. [cited 2023 Sep 4]. Available from: https://www.scidb.cn/en/detail?dataSetId=68f37f29decd4d7b91722657f3e437de..
[15] Brouqui P, Raoult D. Construction, quality control and regulatory aspect of a database of 30,423 COVID-19 patients cared for at the IHU Méditerranée infection France. Biomed J Sci & Tech Res. 52(3):43999–43804..
[16] Lagier JC, Million M, Cortaredona S, Delorme L, Colson P, Fournier PE, et al. Outcomes of 2111 COVID-19 hospitalized patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France, 2020: a monocentric retrospective analysis. Therapeut Clin Risk Manag 2022;18:603–17.
[17] Fichiers des personnes décédées depuis 1970 | Insee [Internet]. [cited 2023 Jun 6]. Available from: https://www.insee.fr/fr/information/4190491.
[18] Mokhtari M, Mohraz M, Gouya MM, Namdari Tabar H, Tabrizi JS, Tayeri K, et al. Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting. Int Immunopharm 2021 Jul 1;96:107636.
[19] Andrade C. Internal, external, and ecological validity in research design, conduct, and evaluation. Indian J Psychol Med 2018;40(5):498–9.
[20] Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. Trav Med Infect Dis 2020 Aug;36:101791.
[21] Rojanaworarit C. Misleading epidemiological and statistical evidence in the presence of simpson's paradox: an illustrative study using simulated scenarios of observational study designs. J Med Life 2020 Mar;13(1):37–44.
[22] Ader F, DisCoVeRy Study Group. An open-label randomized, controlled trial of the effect of lopinavir and ritonavir, lopinavir and ritonavir plus interferon-β-1a, and hydroxychloroquine in hospitalized patients with COVID-19: final results. Clin Microbiol Infect 2022 Sep;28(9):1293–6.
[23] Tsang R, Colley L, Lynd LD. Inadequate statistical power to detect clinically significant differences in adverse event rates in randomized controlled trials. J Clin Epidemiol 2009 Jun;62(6):609–16.

Update

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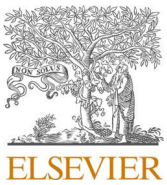

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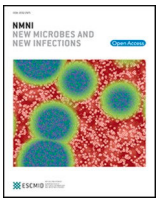

Expression of Concern: 'Outcomes after early treatment with hydroxychloroquine and azithromycin: An analysis of a database of 30,423 COVID-19 patients'

This temporary Expression of Concern relates to the above article.

Concerns have been brought to the attention of the journal regarding potential non-compliance with Elsevier's publishing ethics policies regarding the appropriate conduct of research involving human participants.

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References

[1] Publisher's Note. New Microbes and New Infections 2024;56:101196. https://doi.org/10.1016/j.nmni.2023.101196. ISSN 2052-2975, https://www.sciencedirect.com/science/article/pii/S2052297523001154.

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